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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,110	XU ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,12 and 21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,12 and 21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 January 2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 January 2011 has been entered.

DETAILED ACTION

This Office Action is in response to Applicants' Remarks filed on 10 January 2011. No amendment to the claims were submitted.

Claims 1, 6-8, 12 and 21-34 are pending in the instant application and are examined on the merits herein.

Priority

This application is a National Stage entry of PCT/CN03/00609 filed on 29 July 2003 and claims priority to China foreign application 02125917.8 filed on 2 August 2002. A certified copy of the foreign priority document in Chinese has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 10 January 2011 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Rejections Withdrawn

Applicants' remarks, filed 10 January 2011, with respect to the rejection of claim 22 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, has been fully considered and is persuasive because Applicants have provided documentation showing that it is known in the art that the abbreviation "CODPL" stands for "cyclophosphamide oncovin daunomycin prednione L-asparaginase." This rejection has been **withdrawn**.

In view of Applicants' submission of an English translation of JP 43-025506 to Yamabe in the IDS dated 10 January 2011, the rejections of record in the Office Action dated 8 September 2010 are being withdrawn in favor of the modified grounds of rejections presented below.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011).

Yamabe discloses an esterification reaction to induce one to three fatty acids onto the alcohol moieties of riboflavin. Compared with the tetraesters, these low fatty esters show excellent lipophilicity, and riboflavin content is high in these esters (p. 1, paragraph 2). Additionally, the esters are very easy to hydrolyze to riboflavin in a reaction catalyzed by a lipase (p. 2, first incomplete paragraph). In a study using riboflavin monolaurate, dilaurate, and trilaurate as a substrate in a phosphate buffer solution with pancreas lipase at 37 ℃ for 90 min, it was shown that the hydrolysis rate of riboflavin monolaurate, dilaurate, and trilaurate were 45%, 30% and 27%, respectively (p. 2, paragraph 1 and table on p. 2). Additionally, the substrates showed excellent utility when compared to the control compound (riboflavin) in a study on the nutritional effect of vitamin B2 on rats fed the substrate for two weeks.

It is noted that Yamabe do not expressly teach which hydroxyl position of riboflavin the laurate ester resides on in riboflavin monolaurate. However, based on the disclosed procedure (example 1), and the known fact that in the organic chemistry arts that primary alcohols are significantly more reactive compared to secondary alcohols, it is the Office's position that for riboflavin monolaurate, the lauric ester resides on the 5'-OH as it is the only primary alcohol on the riboflavin chain, as compared to the remaining hydroxyl groups which are located at secondary hydroxyl positions.

It is further noted that Yamabe does not expressly teach that the riboflavin compounds are used for intramuscular injection. However, the recitation "for intramuscular injection" in claim 34 is considered to be an "intended use" of the composition. The "intended use" of a composition will not further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Thus, the disclosure of riboflavin monolaurate by Yamabe, anticipates claims 1 and 34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Section [0001]

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011), in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Yamabe differ from that of the instantly claimed invention in that Yamabe do not expressly teach riboflavin monolaurate as an oil suspension preparation in ethyl oleate.

Remington teaches that the goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then

maintain, the desired drug concentration (p. 1660, column 1, paragraph 1). Different methods of drug delivery include conventional drug therapy and nonimmediate-release drug therapy, which includes delayed release, sustained release, site-specific release and receptor release (p. 1661, column 1, paragraph 1). Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time (p. 1661, column 1, paragraph 30). Advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment (p. 1662, column 2, Table 1). The drug for sustained release may be formulated for oral or parenteral dosage. The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular injections, implants for subcutaneous tissues and various body cavities and transdermal devices (p. 1669, column 2, subheading "Parenteral Dosage Forms"). Intramuscular injections may be in the form of aqueous solutions, complex formation, aqueous suspensions, and oil solutions or oil suspensions (p. 1670-1671). The rate-limiting step in drug release from an aqueous suspension is dissolution (p. 1670, column 1, subheading "Aqueous Suspensions"). In the case of oil solutions, the release rate of a drug is determined by partitioning of the drug out of the oil into the surrounding aqueous medium (p. 1670, column 2, subheading "Oil Solutions and Oil Suspensions"). Drug release from oil suspensions combines the principles involved in aqueous suspensions and oil solutions. The duration of action obtained from oil suspensions is longer than that from oil solutions (p. 1671, column 1, first full paragraph). Examples of

oil solutions and oil suspensions are provided in Tables 10 and 11 wherein the oil component is from sesame oil or cottonseed oil (p. 1671).

The Goldenberg '740 patent teaches the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent. The biologically active agent is incorporated into a polyol/thickened oil suspension, said biologically active agent in the form of a powder or aqueous solution, and said suspension capable of providing for the sustained-release of the biologically active agent (column 3, lines 41-47). The composition is prepared for parenteral administration to a warm blooded animal, wherein said suspension is administered subcutaneously, or intramuscularly, and the biologically active agent is released from the suspension at a controlled rate for up to one week or more (column 3, lines 48-54). The oils used in the composition are biocompatible, of low acidity, and essentially free from rancidity, and are selected from the group consisting of sesame seed, cannola, saffron, castor, cottonseed, olive, peanut, sunflower seed, ethyl oleate, vitamin E, and Miglyol 812 (column 6, lines 57-63).

Wicks *et al.* teach long-acting antiparasitic formulations of doramectin, suitable for injection. The formulation comprises 1-11% w/v of doramectin, in a solvent comprising castor oil at about 25-80% v/v and either (i) ethyl oleate at about 20-75% v/v, or (ii) fractionated coconut oil at about 20-75% v/v, and (iii) optional further auxiliaries (paragraphs 0005-0008). The said formulation has been shown to provide efficacy against economically important endo-parasites at up to 4 months, and ecto-parasites at up to 3 months, following a single injection (paragraph 0013).

Eremin *et al.* teach the replacement of vegetable oils by ethyl oleate in the production of solutions for injection. One of the most important problems of practical pharmacy is the choice of solvents for drugs administered parenterally (p. 1413, paragraph). Water is the most common solvent and is widely used in practice, but a whole series of drugs, such as fat-soluble vitamins, hormones, camphor, etc., are insoluble in it (p. 1413, paragraph 2). Furthermore, water causes the hydrolytic decomposition of a number of substances, accelerating their inactivation. Thus, nonaqueous solvents have been used. Of all the nonaqueous solvents, vegetable oils, ethyl oleate, propylene glycol and polyethyleneglycols with molecular weights of 300 and 400 have the greatest practical value (p. 1413, paragraph 4). In our domestic pharmaceutical chemical factories, nondrying fatty oils, peach and olive oils consisting of mixtures of glycerides of various high molecular-weight acids, are used for the production of various hormone preparations, camphor, and vitamins (p. 1413, paragraph 5). These oils possess a number of disadvantages. They are not well absorbed and they rapidly become rancid, forming peroxides and aldehydes which may lead to the inactivation of the substance. Oily solutions also possess a high viscosity, making administration as an injection difficult. In recent years, ethyl oleate has been widely used for dissolving oleophilic drugs (p. 1413, paragraph 6). Ethyl oleate has some advantages over vegetable oils, it possess a greater dissolving capacity, has a constant chemical composition, is less viscous, and is rapidly absorbed into the tissues (p. 1414, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as ribovflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection. Since Yamabe teach that riboflavin monolaurate has vitamin B2 activity, and has a nutritional effect similar to that of riboflavin, one of ordinary skill in the art would have been motivated to formulate riboflavin monolaurate for drug administration. Since Remington teaches that the advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-monolaurate compound into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils, such as ethyl oleate, results in a prolonged release of the injectable suspension that would provide efficacy from up

to one week to up to four months. Moreover, as disclosed by Eremin *et al.*, ethyl oleate has some advantages over vegetable oils, such as peach and olive oils, in that it possess a greater dissolving capacity, has a constant chemical composition, is less viscous, and is rapidly absorbed into the tissues.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011), in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U), as applied to claim 6, further in view of U.S. Patent No., 5,554,650 to Holl *et al.* (hereinafter referred to as the '650 patent; of record).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102. The teachings of Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* were as described in section [0001] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe, Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* differ from that of the instantly claimed invention in that

the combined teachings of the prior art do not expressly teach riboflavin monolaurate as an oil suspension preparation in ethyl oleate and camellia oil.

The Holl '650 patent teaches an antiphlogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a surfactant, cosurfactant, water, and optionally comprising an oily component, that can exhibit sustained therapeutic levels of diclofenac in plasma (column 1, lines 6-14, lines 60-67). Incorporation of an oily component in the parenteral preparation decreases the peak plasma concentration of diclofenac or its salt after administration, increases the time to achieve peak plasma concentration of diclofenac or its salt after administration, and prolongs the period of time for which diclofenac or its salt remains active (column 3, lines 18-26). One or more oily components can be selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons (column 3, lines 27-30). Preferred are glycerin fatty acid esters that are almond oil, olive oil, sesame oil, peanut oil, fennel oil, camellia oil, corn oil, castor oil, cotton seed oil, and soybean oil, which may be used alone or in combination with one or more oily components (column 3, lines 34-41). The oily components may be incorporated into the parenteral preparation in an amount of about 0.5-30 wt%, preferably 1-15 wt% (column 3, lines 44-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as riboflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of

polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection, with the teachings of the Holl '650 patent, regarding incorporation of an oily component into a parenteral diclofenac preparation to prolong its period of activity after administration. Since the Holl '650 patent teaches that oily components prolong the period at which an administered drug remains active, similar to the teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.*, and further teaches that the oily components can be used in combination with each other, one of ordinary skill in the art would have been motivated to further include additional oily components into the composition, with the expectation that the sustained delivery of the active drug would be maintained. Furthermore, as Remington teaches that the release rate of a drug in an oil solution is determined by partitioning of the drug out of the oil into the surrounding aqueous medium, and the release rate of a drug in an oil suspension is determined by the same factor as an oil solution as well as dissolution of the drug in an aqueous solution, one of ordinary skill in the art would conclude that the different properties of the oily components would affect the release rate of the drug, and thus, different combinations of the oily components, such as ethyl oleate and camellia oil, in different amounts, would also affect the release rate of the drug. As such, based on the combined teachings of the prior art, one of ordinary skill in the art would be able to

make various compositions of riboflavin-5'-monobutyrate in different oily components, in different concentrations, depending on the desired rate of drug release. Furthermore, as Wicks *et al.* suggest that compositions can comprise 20-75% (v/v) ethyl oleate and the Holl '650 patent suggests 0.5-30 wt% of oily components in a composition, it would have been *prima facie* obvious for one of ordinary skill in the art to optimize these amounts so as to obtain the desired rate of drug release for the desired pharmacological properties. The adjustment of particular conventional working conditions (e.g., determining result effective amounts of the ingredients beneficially taught by the cited references, especially within the instantly claimed broad ranges) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of one of ordinary skill in the art. Thus, absent of any evidence to the contrary, it is considered *prima facie* obvious for one of ordinary skill in the art to vary the amounts of ethyl oleate and camellia oil to obtain a composition with the desired pharmacological properties.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 12, 23-26, 29, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011), in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter

referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U), in view of journal article publication by Okuda *et al.* (of record).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Yamabe differ from that of the instantly claimed invention in that Yamabe do not expressly teach that their disclosed compound is formulated as an oil suspension in ethyl oleate. Additionally the teachings of Yamabe differ from that of the instantly claimed invention in that Yamabe do not disclose that their compound and composition are useful in the treatment of ariboflavinosis.

The teachings of Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* were as described in section [0001] above of the claim rejections under 35 USC § 103.

Okuda *et al.* teach nutritional and ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate. To test the nutritional effects of the riboflavin derivatives, rats were fed either a standard diet, a riboflavin-deficient diet, a riboflavin-deficient diet supplemented with riboflavin-5'-monobutyrate suspended in olive oil, or a riboflavin-deficient diet supplemented with riboflavin-5'-monopalmitate suspended in olive oil (p. 9, under subheading "methods"). The authors previously showed that riboflavin tetrabutyrate had the same vitamin B_2 activity (nutritional and ariboflavinosis-curing effects) in young rats as riboflavin, but riboflavin tetrapalmitate did not have vitamin B_2 activity as rats administered riboflavin tetrapalmitate clearly showed

ariboflavinosis. Similar to riboflavin tetrabutyrate, rats fed a diet supplemented with riboflavin-5'-monobutyrate exhibited vitamin B_2 activity (p. 13, second full paragraph). However, rats fed a diet supplemented with riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity. Their results suggest that riboflavin-5'-monobutyrate is easily hydrolyzed to riboflavin, and hence has the same nutritional effect as riboflavin, while riboflavin-5'-monopalmitate was only slowly hydrolyzed to riboflavin (p. 13, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as riboflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate. Since Yamabe teaches that riboflavin monolaurate is hydrolyzed by lipases, and that riboflavin monolaurate has vitamin B2 activity, with a nutritional effect similar to that of riboflavin,

one of ordinary skill in the art would have been motivated to administer riboflavin monolaurate for the treatment of ariboflavinosis, in order to receive the expected benefit, as taught by Okuda *et al.*, that compounds which can be hydrolyzed to riboflavin have vitamin B12 activity and can be used for the treatment of ariboflavinosis. Thus, one of ordinary skill in the art would have a reasonable expectation of success in using riboflavin monolaurate for the treatment of ariboflavinosis.

Additionally, due to its nutritional effect and vitamin B12 activity, one of ordinary skill in the art would have been motivated to formulate riboflavin monolaurate into a drug. Since Remington teaches that the advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-monolaurate compound into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils, such as ethyl oleate, results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months. Moreover, as disclosed by Eremin *et al.*, ethyl oleate has some advantages over vegetable oils, such as peach and olive oils, in that it possess a greater dissolving capacity, has a constant chemical composition, is less viscous, and is rapidly absorbed into the tissues.

With regards to the limitation wherein the drug is administered to an animal that is a human, it is common practice in the pharmaceutical arts to first test drugs in animals, such as rats, before application to humans. Thus, successful *in vivo* testing in rats would marshal resources and direct the expenditure of effort to human clinical trials of the successful compounds, thereby providing an immediate benefit to the public. This is considered to be analogous to the benefit provided by the showing that a drug has *in vivo* utility (see MPEP § 2107.01).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claims 12, 21-25, 27, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011), in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U), in view PG Pub No. US 2003/0105104 A1 by Burzynski (of record), in view of journal publication by McCarthy *et al.* (of record).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Yamabe differ from that of the instantly claimed invention in that Yamabe do not expressly teach that their disclosed compound is formulated as an oil suspension in ethyl oleate. Additionally the teachings of Yamabe differ from that of the instantly claimed invention in that Yamabe do not disclose that their compound and composition are useful in the treatment of digestive tract catarrh.

The teachings of Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* were as described in section [0001] above of the claim rejections under 35 USC § 103.

Burzynski teaches a pharmaceutical composition comprising riboflavin, effectors of the urea cycle, and amino acids, suitably combined with appropriate carriers, diluents, or excipients (abstract; paragraph 0001 and 0008; claim 14), as well as a method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy by administering the said composition to a cancer patient in need thereof (paragraph 0024; claim 1). Common side effects associated with cancer treatment include tiredness, loss of appetite, mucositis, diarrhea and myelosuppression (paragraph 0072). In example 1 (paragraphs 0070-0073), Burzynski shows that when a female patient diagnosed with adenocarcinoma of the colon was administered a composition comprising a sterile solution of six amino acids, L-arginine, and riboflavin prior to treatment by chemotherapy with methotrexate and 5-fluorouracil, the patient did not experience the side effects typically associated with the chemotherapy treatment.

McCarthy *et al.* teach risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract. Oral mucositis is a dose-limiting toxicity of 5-fluorouracil and includes inflammation and ulceration of the oral mucosa and myelosuppression (abstract; p. 484, column 2). Although no direct relationship could be drawn, their results suggest that a lower neutrophil count is associated with the development of oral mucositis during therapy (p. 488, column 2, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as riboflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection, with the teachings of Burzynski, regarding a pharmaceutical composition comprising riboflavin, effectors of the urea cycle and amino acids, with the teachings of McCarthy *et al.*, regarding the risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract catarrh.

Since McCarthy *et al.* teach that digestive tract catarrh and oral mucositis are risk factors of patients undergoing chemotherapy and Burzynski teach that riboflavin can alleviate the toxicity associated with a chemotherapy regimen, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the riboflavin compound taught by Burzynski with a riboflavin ester, such as riboflavin-5'-monolaurate, as taught by Yamabe, with the expectation that riboflavin-5'-monolaurate would treat digestive tract catarrh caused by chemotherapy. It is noted that the Burzynski reference does not specifically teach the administration of ester analogs of riboflavin to cancer patients exhibiting the common side effects of chemotherapy. However, as disclosed by Yamada, the riboflavin esters can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin. Therefore, esters of riboflavin, such as the 5'-laurate monoester of riboflavin, can serve as functional substitutes for natural riboflavin when administered in a composition. Furthermore, it would have *prima facie* obvious to one of ordinary skill in that art that the enhanced lipophilicity of the riboflavin ester due to the presence of the alkyl chain would enhance its migration through lipid bilayers of cells, and thus its bioavailability.

Additionally, due to its nutritional effect and vitamin B12 activity, one of ordinary skill in the art would have been motivated to formulate riboflavin monolaurate into a drug. Since Remington teaches that the advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-monolaurate compound into an oil suspension, such as with

ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils, such as ethyl oleate, results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months. Moreover, as disclosed by Eremin *et al.*, ethyl oleate has some advantages over vegetable oils, such as peach and olive oils, in that it possess a greater dissolving capacity, has a constant chemical composition, is less viscous, and is rapidly absorbed into the tissues.

With regards to the limitation wherein the drug is administered to an animal that is a human, it is common practice in the pharmaceutical arts to first test drugs in animals, such as rats, before application to humans. Thus, successful *in vivo* testing in rats would marshal resources and direct the expenditure of effort to human clinical trials of the successful compounds, thereby providing an immediate benefit to the public. This is considered to be analogous to the benefit provided by the showing that a drug has *in vivo* utility (see MPEP § 2107.01).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0005]

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011),

in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U), in view of journal article publication by Okuda *et al.* (of record), as applied to claims 12, 23-26, 29, 30, further in view of U.S. Patent No. 6,565,891 to Chandra (herein referred to as the '891 patent, of record).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102. The teachings of Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* were as described in section [0001] above of the claim rejections under 35 USC § 103. The teachings of Okuda *et al.* were as described in section [0003] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe, Remington, the Goldenberg '740 patent, Wicks *et al.*, Eremin *et al.*, and Okuda *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art do not expressly teach the administration of a riboflavin monolaurate composition for the treatment of persistent oral ulcer.

The Chandra '891 patent teaches a nutritional supplement for children that is most effective in optimizing health, increasing the immunity, and decreasing the instances and severity of infection, particularly among children (abstract). The importance of each of the component vitamins and minerals making up the nutritional supplement is described in detail. Of particular relevance, is the importance of riboflavin in the nutritional supplement. The Chandra '891 patent teaches that riboflavin

participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain (column 7, lines 22-31). It is used therapeutically to ameliorate ariboflavinosis resulting from diverse causes such as inadequate dietary intake, decreased assimilation, rare genetic defects in the formation of specific flavoproteins, hormonal disorders and after use of certain drugs. Symptoms indicating riboflavin deficiency include rough skin, angular stomatitis, cracked lips, and mouth ulcers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as riboflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of the Chandra '891 patent, regarding the various symptoms of riboflavin deficiency. Since the Chandra '891 patent teaches that oral ulcers are a symptom of riboflavin deficiency,

it is the Office's position that the patient population being treated for ariboflavinosis with a riboflavin ester would necessarily overlap with the patient population that has oral ulcers, and thus would be treated using the same methods.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0006]

Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe (translation provided by Applicants in IDS dated 10 January 2011), in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), in view of Eremin *et al.* (PTO-892, Ref. U), in view of journal article publication by Okuda *et al.* (of record), as applied to claims 12, 23-26, 29, 30, further in view of U.S. Patent No., 5,554,650 to Holl *et al.* (hereinafter referred to as the '650 patent; of record).

The teachings of Yamabe were as disclosed above in the claim rejections under 35 USC § 102. The teachings of Remington, the Goldenberg '740 patent, Wicks *et al.*, and Eremin *et al.* were as described in section [0001] above of the claim rejections under 35 USC § 103. The teachings Okuda *et al.* were as described in section [0003] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe, Remington, the Goldenberg '740 patent, Wicks *et al.*, Eremin *et al.*, and Okuda *et al.* differ from that of the instantly claimed

invention in that the combined teachings of the prior art do not expressly teach riboflavin monolaurate as an oil suspension preparation in ethyl oleate and camellia oil.

The teachings of the Holl '650 patent were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe, concerning riboflavin comprising one to three fatty acids, such as riboflavin monolaurate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Eremin *et al.*, regarding the substitution of vegetable oils with ethyl oleate in the production of solutions for injection, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of the Holl '650 patent, regarding incorporation of an oily component into a parenteral diclofenac preparation to prolong its period of activity after administration. Since the Holl '650 patent teaches that oily components prolong the period at which an administered drug remains active, similar to the teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.*, and further teaches that the oily components

can be used in combination with each other, one of ordinary skill in the art would have been motivated to further include additional oily components into the composition, with the expectation that the sustained delivery of the active drug would be maintained. Furthermore, as Remington teaches that the release rate of a drug in an oil solution is determined by partitioning of the drug out of the oil into the surrounding aqueous medium, and the release rate of a drug in an oil suspension is determined by the same factor as an oil solution as well as dissolution of the drug in an aqueous solution, one of ordinary skill in the art would conclude that the different properties of the oily components would affect the release rate of the drug, and thus, different combinations of the oily components, such as ethyl oleate and camellia oil, in different amounts, would also affect the release rate of the drug. As such, based on the combined teachings of the prior art, one of ordinary skill in the art would be able to make various compositions of riboflavin-5'-monobutyrate in different oily components, in different concentrations, depending on the desired rate of drug release. Furthermore, as Wicks *et al.* suggest that compositions can comprise 20-75% (v/v) ethyl oleate and the Holl '650 patent suggests 0.5-30 wt% of oily components in a composition, it would have been *prima facie* obvious for one of ordinary skill in the art to optimize these amounts so as to obtain the desired rate of drug release for the desired pharmacological properties. The adjustment of particular conventional working conditions (e.g., determining result effective amounts of the ingredients beneficially taught by the cited references, especially within the instantly claimed broad ranges) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of one of

ordinary skill in the art. Thus, absent of any evidence to the contrary, it is considered *prima facie* obvious for one of ordinary skill in the art to vary the amounts of ethyl oleate and camellia oil to obtain a composition with the desired pharmacological properties.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments filed 10 January 2011 with respect to the rejection of the claims in the Office Action dated 8 September 2010 have been fully considered but are moot in view of the new ground(s) of rejection.

To the extent that Applicants' arguments are still applicable to the instant claims, Applicants argue that one of ordinary skill in the art would not have picked riboflavin trilaurate or riboflavin 5'-palmitate as a lead compound at the time of the invention for modification because riboflavin 5'-palmitate was shown to have little or no vitamin B12 activity. Applicants argue that riboflavin trilaurate is more similar in length to riboflavin 5'-palmitate than riboflavin 5'-butyrate of tetrabutyrate, which were shown to have vitamin B12 activity. Thus, one of ordinary skill in the art would not expect riboflavin trilaurate to have activity, and would have thus picked riboflavin 5'-butyrate of tetrabutyrate for modification. Applicants' arguments have been fully considered but are not persuasive in view of the modified rejections applied above using the translation of JP 43-025506 to Yamabe which discloses riboflavin monolaurate as having nutritional effects and vitamin B12 activity.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is (571)270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/SCARLETT GOON/
Examiner
Art Unit 1623